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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: NOVEL TRICYCLIC SPIRODERIVATIVES AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

(57) Abstract: The invention provides compounds of formula (I) wherein m, R^1, n, R^2, q, X, Y, Z, R^3, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in the specification, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 101244-1 WO	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/SE 2004/001476	International filing date (day/month/year) 14 October 2004	(Earliest) Priority Date (day/month/year) 17 October 2003
Applicant ASTRAZENECA AB ET AL		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

Novel tricyclic spiroderivatives as modulators of chemokine receptor activity.

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the drawings to be published with the abstract is Figure No. -

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

Novel tricyclic spiroderivatives as modulators of chemokine receptor activity.

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

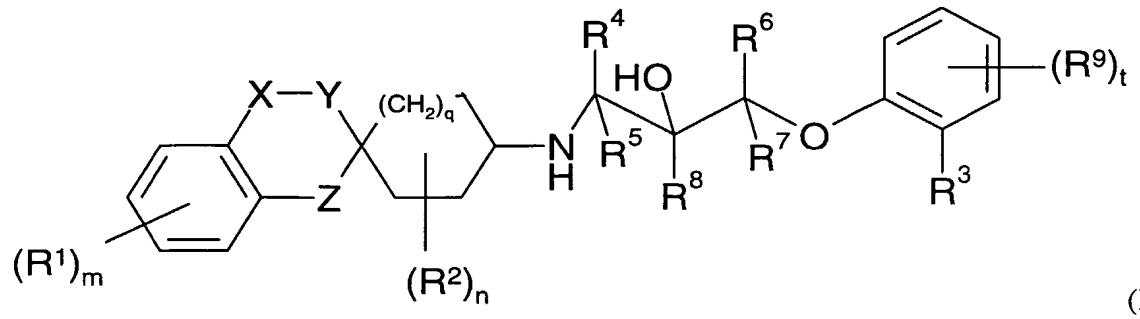
Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C) and Cys-Cys (C-C) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

In accordance with the present invention, there is therefore provided a compound of formula



(I)

wherein

m is 0, 1, 2, 3 or 4;

each R^1 independently represents halogen, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy or sulphonamido ($-SO_2NH_2$);

either X represents a bond, $-CH_2-$, -O- or -C(O)- and Y represents a bond, $-CH_2-$, -O- or -C(O)-, or X and Y together represent a group $-CH=C(CH_3)-$ or $-C(CH_3)=CH-$, and Z represents a bond, -O-, -NH- or $-CH_2-$, provided that only one of X, Y and Z can represent a bond at any one time and provided that X and Y do not both simultaneously represent –O- or -C(O)-;

n is 0, 1 or 2;

each R^2 independently represents halogen or C_1-C_6 alkyl;

q is 0 or 1;

R^3 represents $-NHC(O)R^{10}$, $-C(O)NR^{11}R^{12}$ or $-COOR^{12a}$;

R^4, R^5, R^6, R^7 and R^8 each independently represent a hydrogen atom or a C_1-C_6 alkyl group;

t is 0, 1 or 2;

each R^9 independently represents halogen, cyano, hydroxyl, carboxyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, or C_1-C_6 alkyl optionally substituted by at least one substituent selected from carboxyl and C_1-C_6 alkoxycarbonyl;

R^{10} represents a group C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, adamantyl, C_5-C_6 cycloalkenyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and

sulphur, each of which may be optionally substituted by one or more substituents independently selected from nitro, hydroxyl, oxo, halogen, carboxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, phenyl and -NHC(O)-R^{13}, or

R^{10} represents a group $-NR^{14}R^{15}$ or $-O-R^{16}$;

R^{11} and R^{12} each independently represent (i) a hydrogen atom, (ii) a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur and optionally further comprising a bridging group, the ring being optionally substituted with at least one substituent selected from halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl and C_1-C_6 haloalkyl,
(iii) a C_1-C_6 alkyl group optionally substituted by at least one substituent selected from halogen, amino ($-NH_2$), hydroxyl, C_1-C_6 haloalkyl, carboxyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkylcarbonylamino and a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur and optionally further comprising a bridging group, the ring being optionally substituted with at least one substituent selected from halogen, hydroxyl, oxo (=O), C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl and C_1-C_6 haloalkyl, or
(iv) C_1-C_6 alkylsulphonyl, or
R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom and that is optionally fused to a benzene ring to form a 8- to 11-membered ring system, the heterocyclic ring or ring system being optionally substituted with at least one substituent selected from halogen, hydroxyl, amido ($-CONH_2$), C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonylamino, C_1-C_6 alkylaminocarbonyl, di-C_1-C_6 alkylaminocarbonyl, phenyl, halophenyl, phenylcarbonyl, phenylcarbonyloxy and hydroxydiphenylmethyl;

R^{12a} represents a hydrogen atom or a C_1-C_6 alkyl group;

R^{13} represents a C_1-C_6 alkyl, amino ($-NH_2$) or phenyl group;

R^{14} and R^{15} each independently represent a hydrogen atom, or a group C_1-C_6 alkyl, C_1-C_6 alkylsulphonyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted as defined above for R^{10}, or

R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom, the heterocyclic ring being optionally substituted by at least one hydroxyl; and

R^{16} represents a hydrogen atom, or a group C_1-C_6 alkyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted as defined above for R^{10};

or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, unless otherwise stated, an alkyl or alkenyl substituent group or an alkyl moiety in a substituent group may be linear or branched. The alkyl moieties in a di-alkylamino or di-alkylaminocarbonyl substituent group may be the same or different. A haloalkyl or halophenyl substituent group will comprise at least one halogen atom, e.g. one, two, three or four halogen atoms. A hydroxyalkyl substituent may contain one or more hydroxyl groups but preferably contains one or two hydroxyl groups. In the ring substituted by R^2, R^2 may be attached to any suitable ring carbon atom including the carbon atom of $(CH_2)_q$. When R^{11} and R^{12} or R^{14} and R^{15} represent a 4- to 7-membered saturated heterocycle, it should be understood that the heterocycle will contain no more than two ring heteroatoms: the nitrogen ring atom to which R^{11} and R^{12} or R^{14} and R^{15} are attached and optionally a nitrogen, oxygen or sulphur ring atom. In the definition of R^{10} (or R^{14}, R^{15} or R^{16}) it should be noted that the saturated or unsaturated 5- to 10-membered heterocyclic ring system may have alicyclic or aromatic properties. Similarly, in the definition of R^{11} or R^{12}, a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom may have alicyclic or aromatic properties. An unsaturated ring system will be partially or fully unsaturated.

In an embodiment of the invention, m is 0 or 1.

Each R^1 independently represents halogen (e.g. chlorine, fluorine, bromine or iodine), cyano, hydroxyl, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, haloalkyl (e.g. trifluoromethyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy) or sulphonamido.

In an embodiment of the invention, each R^1 independently represents halogen, C_1-C_6, preferably C_1-C_4, alkyl or C_1-C_6, preferably C_1-C_4, haloalkyl.

In another embodiment, each R^1 independently represents fluorine, chlorine, methyl or trifluoromethyl, particularly chlorine.

Combinations of X and Y of particular interest include any one or more of the following:

X	Y
bond	O
O	bond
CH_2	bond
bond	CH_2
CH_2	O
O	CH_2
C(O)	O
O	C(O)
CH_2	CH_2
-CH=C(CH_3)-	

In an embodiment of the invention, X and Y have the meanings shown below:

X	Y
bond	O
O	bond
CH_2	O
O	CH_2
C(O)	O
O	C(O)
CH_2	CH_2
-CH=C(CH_3)-	

In a further embodiment, X and Y have the meanings shown below:

X	Y
bond	O
O	bond
CH_2	bond
bond	CH_2

In an embodiment of the invention, Z represents a bond, -O- or $-CH_2-$.

Combinations of X, Y and Z of particular interest include any one or more of the following:

X	Y	Z
bond	O	CH_2
O	bond	CH_2
CH_2	bond	O
bond	CH_2	O
CH_2	O	bond
C(O)	O	bond
O	C(O)	bond
CH_2	CH_2	bond
O	bond	O
bond	O	O
CH_2	CH_2	O
O	CH_2	CH_2
-CH=C(CH_3)-		bond

In an embodiment of the invention, X, Y and Z have the meanings shown below:

X	Y	Z
bond	O	CH_2
O	bond	CH_2
CH_2	O	bond
O	CH_2	bond
C(O)	O	bond
O	C(O)	bond
CH_2	CH_2	bond
bond	O	O
O	bond	O
-CH=C(CH_3)-		bond

In another embodiment of the invention, X, Y and Z have the meanings shown below:

X	Y	Z
bond	O	CH_2
O	bond	CH_2
CH_2	bond	O
bond	CH_2	O

Each R^2 independently represents halogen (e.g. chlorine, fluorine, bromine or iodine) or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

In an embodiment of the invention, n is 1 and R^2 represents halogen, particularly fluorine.

In an embodiment of the invention, R^3 represents -NHC(O)R^{10}.

In another embodiment of the invention, R^3 represents -C(O)N$R^{11}R^{12}$.

R^4, R^5, R^6, R^7 and R^8 each independently represent a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

In an embodiment of the invention, R^4, R^5, R^6, R^7 and R^8 each independently represent a hydrogen atom or a methyl group.

In another embodiment of the invention, R^4, R^5, R^6 and R^7 each represent a hydrogen atom and R^8 represents a methyl group.

In an embodiment of the invention, R^4, R^5, R^6, R^7 and R^8 each represent a hydrogen atom.

In an embodiment of the invention, t is 0, 1 or 2, particularly 0 or 1.

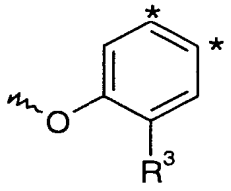
Each R^9 independently represents halogen (e.g. chlorine, fluorine, bromine or iodine), cyano, hydroxyl, carboxyl, C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl or n-butoxycarbonyl), C_1-C_6, preferably C_1-C_4, haloalkyl (e.g. trifluoromethyl), orC_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents) independently selected from carboxyl and C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl or n-butoxycarbonyl).

In an embodiment of the invention, each R^9 independently represents halogen, cyano, hydroxyl, carboxyl, C_1-C_6, preferably C_1-C_4, alkoxy, C_1-C_6, preferably C_1-C_4, alkoxycarbonyl, C_1-C_6, preferably C_1-C_4, haloalkyl or C_1-C_6, preferably C_1-C_4, alkyl.

In another embodiment of the invention, each R^9 independently represents halogen, hydroxyl, carboxyl, methyl, methoxy, methoxycarbonyl or trifluoromethyl.

In a further embodiment, each R^9 independently represents halogen (particularly fluorine) or hydroxyl.

R^9 is preferably bound to a carbon atom located in the *para* position with respect to the carbon atom to which either the oxygen atom or the group R^3 is bound, as indicated by the asterisks in the partial structure shown below:



R^{10} may represent a group C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_2-C_6, preferably C_2-C_4, alkenyl, C_3-C_6 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), adamantyl, C_5-C_6 cycloalkenyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each of which (i.e. each of the recited groups and the ring system) may be optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from nitro, hydroxyl, oxo, halogen (e.g. fluorine, chlorine, bromine or iodine), carboxyl, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkylthio (e.g. methylthio or ethylthio), C_1-C_6, preferably C_1-C_4, alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), phenyl and -NHC(O)-R^{13}.

The saturated or unsaturated 5- to 10-membered heterocyclic ring system in R^{10} may be monocyclic or polycyclic (e.g. bicyclic), examples of which include pyrrolidinyl, piperidinyl, pyrazolyl, thiazolidinyl, thienyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, quinolinyl, benzimidazolyl, triazolyl, tetrazolyl, pyridinyl and combinations of any two or more thereof.

In an embodiment of the invention, R^{10} represents a group C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl or a saturated or unsaturated 5- to 6-membered heterocyclic ring system comprising at least one ring heteroatom (e.g. one or two ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each of which (i.e. each of the recited groups and the ring system) may be optionally substituted by one, two, three or four substituents independently selected from nitro, hydroxyl, oxo, halogen, carboxyl, C_1-C_6, preferably C_1-C_4, alkyl, C_1-C_6, preferably C_1-C_4, alkoxy, C_1-C_6, preferably C_1-C_4, alkylthio,

C_1-C_6, preferably C_1-C_4, alkylcarbonyl, C_1-C_6, preferably C_1-C_4, alkoxycarbonyl, phenyl and -NHC(O)-R^{13}.

In another embodiment of the invention, R^{10} represents a group C_1-C_6 alkyl, C_3-C_6 cycloalkyl or phenyl, each of which may be optionally substituted by one or two substituents independently selected from halogen, C_1-C_6, preferably C_1-C_4, alkyl and C_1-C_6, preferably C_1-C_4, alkoxy.

In still another embodiment of the invention, R^{10} represents C_1-C_6 alkyl, cyclopentyl or phenyl, particularly C_1-C_6 alkyl.

Alternatively, R^{10} may represent a group $-NR^{14}R^{15}$ or $-O-R^{16}$.

R^{14} and R^{15} each independently represent a hydrogen atom, or a group C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkylsulphonyl (e.g. methylsulphonyl, ethylsulphonyl, n-propylsulphonyl, isopropylsulphonyl, n-butylsulphonyl, isobutylsulphonyl, tert-butylsulphonyl, n-pentylsulphonyl or n-hexylsulphonyl), phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each group (i.e. each of the recited groups including the ring system) being optionally substituted as defined above for R^{10} (that is, optionally substituted with one or more (e.g. one, two, three or four) substituents independently selected from nitro, hydroxyl, oxo, halogen (e.g. fluorine, chlorine, bromine or iodine), carboxyl, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkylthio (e.g. methylthio or ethylthio), C_1-C_6, preferably C_1-C_4, alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or

n-hexylcarbonyl), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), phenyl and -NHC(O)-R^{13}),
or R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom (e.g. pyrrolidinyl, piperidinyl, morpholino, piperazinyl or thiomorpholinyl), the heterocyclic ring being optionally substituted by at least one hydroxyl (e.g. one or two hydroxyls).

In R^{14} or R^{15}, the saturated or unsaturated 5- to 10-membered heterocyclic ring system may be monocyclic or polycyclic (e.g. bicyclic), examples of which include pyrrolidinyl, piperidinyl, pyrazolyl, thiazolidinyl, thienyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, quinolinyl, benzimidazolyl, triazolyl, tetrazolyl, pyridinyl and combinations of any two or more thereof.

In an embodiment of the invention, R^{14} and R^{15} each independently represent a hydrogen atom or a C_1-C_6 alkyl or C_1-C_6 alkylsulphonyl group, each group being optionally substituted as defined above for R^{10}, or R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 5- to 6-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom, the heterocyclic ring being optionally substituted by at least one hydroxyl.

In a further embodiment, R^{14} and R^{15} each independently represent a hydrogen atom or a C_1-C_6 alkylsulphonyl group, or R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 5- to 6-membered saturated heterocyclic ring that is optionally substituted by at least one hydroxyl.

In a still further embodiment, R^{14} and R^{15} each independently represent a hydrogen atom or a methylsulphonyl group, or R^{14} and R^{15} together with the nitrogen atom to which they are attached form a pyrrolidinyl or piperidinyl ring optionally substituted by one hydroxyl group.

R^{16} represents a hydrogen atom, or a group C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each group (i.e. each of the recited groups including the ring system) being optionally substituted as defined above for R^{10} (that is, optionally substituted with one or more (e.g. one, two, three or four) substituents independently selected from nitro, hydroxyl, oxo, halogen (e.g. fluorine, chlorine, bromine or iodine), carboxyl, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkylthio (e.g. methylthio or ethylthio), C_1-C_6, preferably C_1-C_4, alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), phenyl and -NHC(O)-R^{13}).

In R^{16}, the saturated or unsaturated 5- to 10-membered heterocyclic ring system may be monocyclic or polycyclic (e.g. bicyclic), examples of which include pyrrolidinyl, piperidinyl, pyrazolyl, thiazolidinyl, thienyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, quinolinyl, benzimidazolyl, triazolyl, tetrazolyl, pyridinyl and combinations of any two or more thereof.

R^{11} and R^{12} each independently represent

(i) a hydrogen atom,

(ii) a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur and optionally further comprising a bridging group (examples of which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, phenyl, pyrolyl, imidazolyl, pyridinyl, pyrazinyl, pyridazinyl,

tetrazolyl, pyrimidinyl, thienyl, furanyl, tetrahydrofuranyl and combinations of any two or more thereof), the ring being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, C_1-C_6, preferably C_1-C_5, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 1,1-dimethylpropyl or n-hexyl), C_1-C_6, preferably C_1-C_4, hydroxyalkyl (e.g. $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ or $-CH(OH)CH_3$) and C_1-C_6, preferably C_1-C_4, haloalkyl (e.g. trifluoromethyl),

(iii) a C_1-C_6 alkyl group optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), amino ($-NH_2$), hydroxyl, C_1-C_6, preferably C_1-C_4, haloalkyl (e.g. trifluoromethyl), carboxyl, C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), C_1-C_6, preferably C_1-C_4, alkylcarbonylamino (e.g. methylcarbonylamino or ethylcarbonylamino) and a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur and optionally further comprising a bridging group (examples of which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, phenyl, pyrolyl, imidazolyl, pyridinyl, pyrazinyl, pyridazinyl, tetrazolyl, pyrimidinyl, thienyl, furanyl, tetrahydrofuranyl and combinations of any two or more thereof), the ring being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, oxo (=O), C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, hydroxyalkyl (e.g. $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ or $-CH(OH)CH_3$) and C_1-C_6, preferably C_1-C_4, haloalkyl (e.g. trifluoromethyl), or

(iv) C_1-C_6, preferably C_1-C_4, alkylsulphonyl (e.g. methylsulphonyl or ethylsulphonyl), or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen,

oxygen or sulphur atom (e.g. pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or thiomorpholinyl) and that is optionally fused to a benzene ring to form a 8- to 11-membered ring system (e.g. dihydroisoquinolinyl or dihydroisoindolyl), the heterocyclic ring or ring system being optionally substituted with at least one substituent (e.g. one, two,three or four substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, amido ($-CONH_2$), C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, hydroxyalkyl (e.g. $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ or $-CH(OH)CH_3$), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), C_1-C_6, preferably C_1-C_4, haloalkyl (e.g. trifluoromethyl), C_1-C_6, preferably C_1-C_4, alkylamino (e.g. methylamino or ethylamino), di-C_1-C_6, preferably C_1-C_4, alkylamino (e.g. dimethylamino), C_1-C_6, preferably C_1-C_4, alkylcarbonyl (e.g. methylcarbonyl or ethylcarbonyl), C_1-C_6, preferably C_1-C_4, alkylcarbonylamino (e.g. methylcarbonylamino or ethylcarbonylamino), C_1-C_6, preferably C_1-C_4, alkylaminocarbonyl (e.g. methylaminocarbonyl or ethylaminocarbonyl), di-C_1-C_6, preferably C_1-C_4, alkylaminocarbonyl (e.g. dimethylaminocarbonyl), phenyl, halophenyl (e.g. fluorophenyl or chlorophenyl), phenylcarbonyl, phenylcarbonyloxy and hydroxydiphenylmethyl.

In an embodiment of the invention, R^{11} and/or R^{12} represents a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur and optionally further comprising a bridging group, the ring being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, C_1-C_6, preferably C_1-C_5, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 1,1-dimethylpropyl or n-hexyl) and C_1-C_6, preferably C_1-C_4, hydroxyalkyl (e.g. $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ or $-CH(OH)CH_3$).

In a further embodiment of the invention, R^{11} and/or R^{12} represents a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring nitrogen atom and optionally further comprising a bridging group (in particular, cyclopropyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, phenyl, pyrrolidinyl and tetrazolyl), the ring being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, C_1-C_5 alkyl and C_1-C_2 hydroxyalkyl.

In an embodiment of the invention, R^{11} and/or R^{12} represents a C_1-C_6 alkyl group optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from amino, hydroxyl, C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), C_1-C_6, preferably C_1-C_4, alkylcarbonylamino (e.g. methylcarbonylamino or ethylcarbonylamino) and a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen and oxygen and optionally further comprising a bridging group, the ring being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, oxo, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, hydroxyalkyl (e.g. $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ or $-CH(OH)CH_3$) and C_1-C_6, preferably C_1-C_4, haloalkyl (e.g. trifluoromethyl).

In another embodiment of the invention, R^{11} and/or R^{12} represents a C_1-C_6 alkyl group optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from amino, hydroxyl, C_1-C_4 alkoxy, C_1-C_2 alkoxycarbonyl, C_1-C_2 alkylcarbonylamino and a 3- to 6-membered saturated or unsaturated ring optionally comprising one or two ring heteroatoms selected from nitrogen and oxygen and optionally further comprising a bridging group (in particular, cyclopropyl, bicyclo[2.2.1]heptyl, phenyl or tetrahydrofuranyl), the ring being optionally substituted

with at least one substituent (e.g. one, two or three substituents independently) selected from oxo (e.g. to form a 2,5-dioxoimidazolidinyl ring) and C_1-C_2 alkyl.

In an embodiment of the invention, R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom (e.g. pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or thiomorpholinyl) and that is optionally fused to a benzene ring to form a 8- to 11-membered ring system (e.g. dihydroisoquinolinyl or dihydroisoindolyl), the heterocyclic ring or ring system being optionally substituted with at least one substituent (e.g. one, two,three or four substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, amido, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, hydroxyalkyl (e.g. $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ or $-CH(OH)CH_3$), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), C_1-C_6, preferably C_1-C_4, haloalkyl (e.g. trifluoromethyl), di-C_1-C_6, preferably C_1-C_4, alkylamino (e.g. dimethylamino), C_1-C_6, preferably C_1-C_4, alkylcarbonylamino (e.g. methylcarbonylamino or ethylcarbonylamino), di-C_1-C_6, preferably C_1-C_4, alkylaminocarbonyl (e.g. dimethylaminocarbonyl), phenyl, halophenyl (e.g. fluorophenyl or chlorophenyl), phenylcarbonyloxy and hydroxydiphenylmethyl.

In an embodiment of the invention, R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 5- to 6-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom and that is optionally fused to a benzene ring to form a 9- to 10-membered ring system, the heterocyclic ring or ring system being optionally substituted with one or two substituents independently selected from fluorine, hydroxyl, amido, C_1-C_2 alkyl, C_1-C_2 hydroxyalkyl, C_1-C_2 alkoxy, C_1-C_2 alkoxycarbonyl, C_1-C_2 haloalkyl, di-C_1-C_2 alkylamino,

C_1-C_2 alkylcarbonylamino, di-C_1-C_2 alkylaminocarbonyl, phenyl, chlorophenyl, phenylcarbonyloxy and hydroxydiphenylmethyl.

In another embodiment of the invention, R^{11} and R^{12} together with the nitrogen atom to which they are attached form a heterocyclic ring or ring system selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dihydroisoquinolinyl and dihydroisoindolyl, the heterocyclic ring or ring system being optionally substituted with one or two substituents independently selected from fluorine, hydroxyl, amido, methyl, hydroxymethyl, 2-hydroxyethyl, methoxy, methoxycarbonyl, trifluoromethyl, dimethylamino, methylcarbonylamino, dimethylaminocarbonyl, phenyl, chlorophenyl, phenylcarbonyloxy and hydroxydiphenylmethyl.

R^{12a} represents a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) group.

In an embodiment of the invention, R^{12a} represents a hydrogen atom or methyl group.

R^{13} represents a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), amino or phenyl group.

In an embodiment of the invention:

m is 1;

R^1 represents halogen;

X represents a bond, $-CH_2-$ or -O-, Y represents a bond, $-CH_2-$ or -O- and Z represents $-CH_2-$ or -O-, provided that X, Y and Z are different to one another;

n is 0;

q is 1;

R^3 represents $-NHC(O)R^{10}$ or $-C(O)NR^{11}R^{12}$;

R^4, R^5, R^6, R^7 and R^8 each represent hydrogen or methyl;

t is 0 or 1;

R^9 represents halogen or hydroxyl;

R^{10} represents methyl; and

R^{11} and R^{12} each independently represent hydrogen or methyl.

Examples of compounds of the invention include:

2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-hydroxy-*N*-methylbenzamide,

N-2-({(2S)-3-[5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-fluorophenyl]acetamide,

2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-*N*-methylbenzamide,

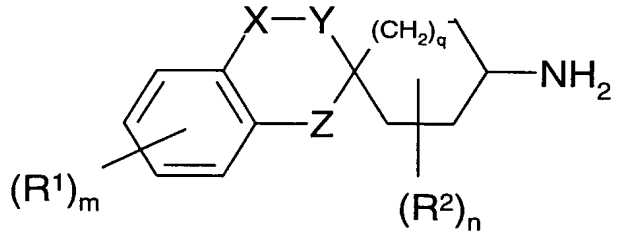
N-[2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-hydroxyphenyl]acetamide,

N-[2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxy-2-methylpropyl}oxy)-4-hydroxyphenyl]acetamide (trifluoro acetate),

and pharmaceutically acceptable salts and solvates of any one thereof.

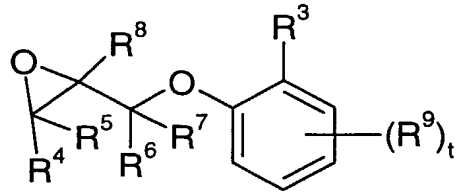
The present invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined above which comprises,

(a) reacting a compound of formula



(II)

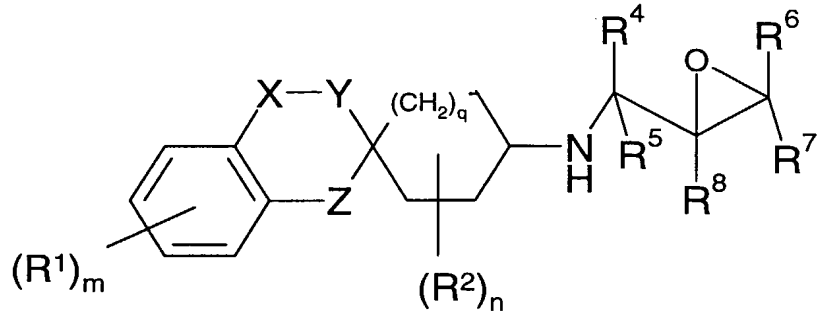
wherein m, R^1, n, R^2, q, X, Y and Z are as defined in formula (I), with a compound of formula



(III)

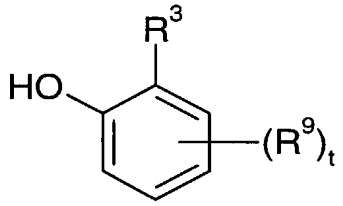
wherein R^3, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in formula (I); or

(b) reacting a compound of formula



(IV)

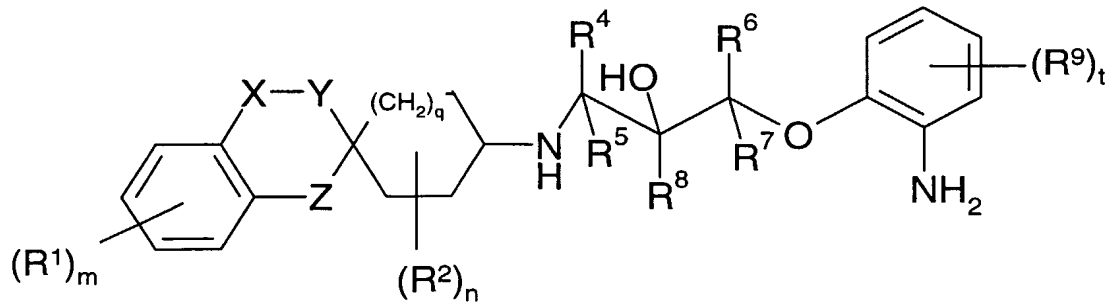
wherein m, R^1, n, R^2, q, X, Y, Z, R^4, R^5, R^6, R^7 and R^8 are as defined in formula (I), with a compound of formula



(V)

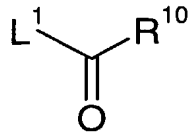
wherein R^3, t and R^9 are as defined in formula (I), in the presence of a suitable base; or

(c) when R^3 represents -NHC(O)R^{10}, reacting a compound of formula



(VI)

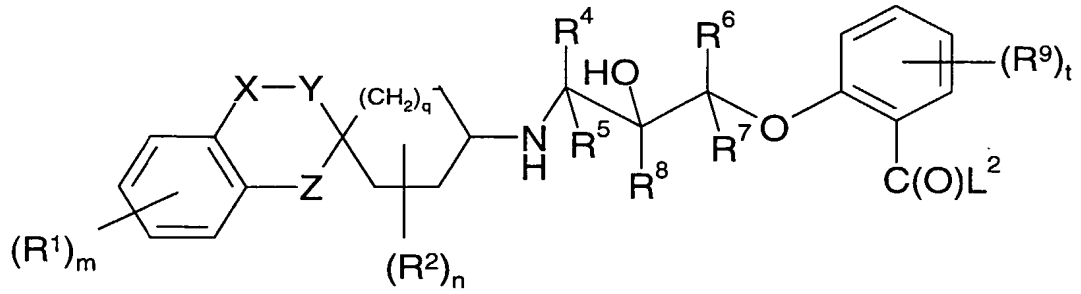
wherein m, R^1, n, R^2, q, X, Y, Z, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in formula (I), with a compound of formula



(VII)

wherein L^1 represents a leaving group (e.g. a hydroxyl group or a halogen atom such as chlorine) and R^{10} is as defined in formula (I); or

(d) when R^3 represents $-C(O)NR^{11}R^{12}$, reacting a compound of formula



(VIII)

wherein L^2 represents a leaving group (e.g. a hydroxyl group or a halogen atom such as chlorine) and m, R^1, n, R^2, q, X, Y, Z, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in formula (I), with a compound of formula (IX), $NHR^{11}R^{12}$, wherein R^{11} and R^{12} are as defined in formula (I); or

(e) when R^3 represents $-NHC(O)R^{10}$, R^{10} represents $-NR^{14}R^{15}$ and R^{14} and R^{15} both represent hydrogen, reacting a compound of formula (VI) as defined in (c) above with potassium cyanate;

and optionally after (a), (b), (c), (d) or (e) forming a pharmaceutically acceptable salt or solvate.

The processes of the invention may conveniently be carried out in a solvent, e.g. an organic solvent such as an alcohol (e.g. methanol or ethanol), a hydrocarbon (e.g. toluene) or tetrahydrofuran, dimethylformamide, N-methylpyrrolidinone or acetonitrile at a temperature of, for example, 0°C or above such as a temperature in the range from 0, 5, 10, 15 or 20°C to 100, 110 or 120°C.

Compounds of formulae (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) are either commercially available, are known in the literature or may be prepared using known techniques.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the reagents may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

Compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. Enantiomerically pure forms are particularly desired.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially MIP-1α chemokine receptor) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative and hyperproliferative

diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS).

Examples of these conditions are:

(1) **(the respiratory tract)** airways diseases including chronic obstructive pulmonary disease (COPD) such as irreversible COPD; asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic

syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura;

(6) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(7) cancers, especially non-small cell lung cancer (NSCLC) and squamous sarcoma;

(8) diseases in which angiogenesis is associated with raised chemokine levels; and

(9) cystic fibrosis, stroke, re-perfusion injury in the heart, brain, peripheral limbs and sepsis.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention also provides a method of treating an inflammatory disease which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

The invention still further provides a method of treating an airways disease which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I) may be in the range from 0.001 mg/kg to 30 mg/kg.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane

aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

The invention will now be further explained by reference to the following illustrative examples, in which ^{1}H NMR spectra were recorded on Varian Unity Inova 400. The central solvent peak of chloroform–*d* (δ_H 7.27 ppm), acetone-d_6 (δ_H 2.05 ppm), DMSO-d_6 (δ_H 2.50 ppm), or methanol-d_4 (δ_H 4.87 ppm) were used as internal standard. Low resolution mass spectra and accurate mass determination were recorded on a Hewlett-Packard 1100 LC-MS system equipped with APCI /ESI ionisation chambers.
All solvents and commercial reagents were laboratory grade and used as received.
The nomenclature used for the compounds was generated with ACD/IUPAC Name Pro.
The abbreviations or terms used in the examples have the following meanings:

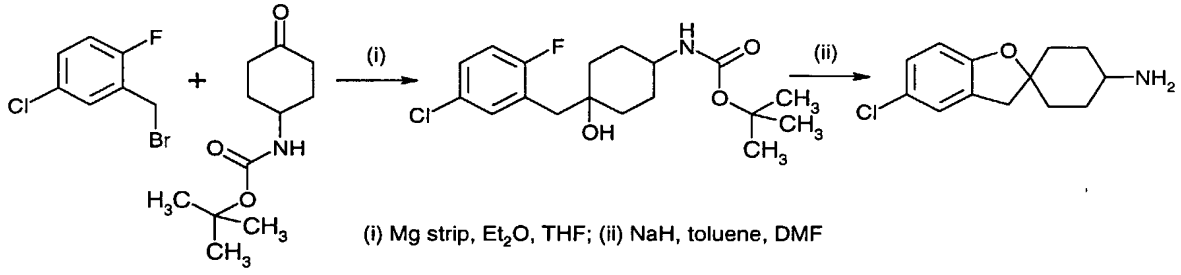
THF	:	tetrahydrofuran
NH_4Cl	:	ammonium chloride
Na_2SO_4	:	sodium sulphate
NaH	:	sodium hydride
DMF	:	*N,N*-dimethylformamide
H_2O	:	water
CF_3CO_2H	:	trifluoroacetic acid
K_2CO_3	:	potassium carbonate
CH_2Cl_2	:	dichloromethane
NH_4OH	:	ammonium hydroxide
CH_3CN	:	acetonitrile
psi	:	pounds per square inch
Cs_2CO_3	:	caesium carbonate
HCl	:	hydrochloric acid
$NaHCO_3$	:	sodium hydrogencarbonate
Et_3N	:	triethylamine

DMAP : 4-dimethylaminopyridine

NaOEt : sodium ethoxide

Examples

Intermediate compound: (5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amine



(i) Mg strip, Et_2O, THF; (ii) NaH, toluene, DMF

Step I

***tert*-Butyl[4-(5-chloro-2-fluorobenzyl)-4-hydroxycyclohexyl]carbamate**

To a suspension of magnesium strip (283.6 mg, 11.67 mmol) in diethyl ether (4 mL) was added a piece of iodine followed by 0.3 mL of 2-(bromomethyl)-4-chloro-1-fluorobenzene under nitrogen atmosphere. A high intensity heat gun was applied to initiate the reaction, then 2-(bromomethyl)-4-chloro-1-fluorobenzene (2.61 g, 11.67 mmol) in diethyl ether (4.5 mL) was added slowly at such a speed that a gentle reflux was maintained. After the addition was completed, the reaction mixture was refluxed for 3 hours, cooled to room temperature and a solution of tert-butyl (4-oxocyclohexyl)carbamate (2.49 g, 11.67 mmol) in diethyl ether (9 mL) and THF (9 mL) was added slowly with vigorous stirring. After the addition was completed, the reaction mixture was left at room temperature for 3 hours. Aqueous NH_4Cl (20 mL) was added and the mixture was stirred at room temperature overnight, extracted with ethyl acetate, washed with H_2O, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel flash chromatography (0-30%ethyl acetate in petroleum benzene) to give the subtitled compound (1.4 g).

Step II

(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amine

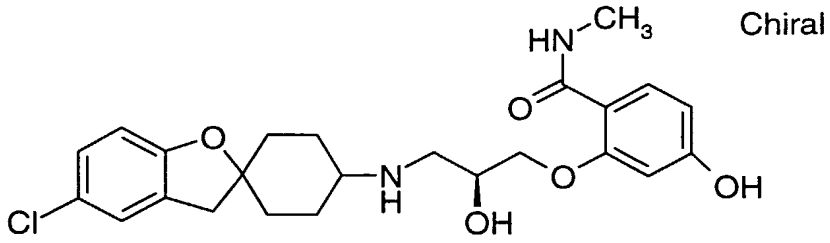
A mixture of *tert*-butyl[4-(5-chloro-2-fluorobenzyl)-4-hydroxycyclohexyl] carbamate (1.4 g, 3.91 mmol) and NaH (55%, 511 mg, 11.73 mmol) in toluene (21 mL) was heated at 110 ^{0}C for 5 minutes. DMF (7 mL) was added and the mixture was stirred at 110 ^{0}C for 30 minutes before allowing to cool to room temperature. The reaction mixture was partitioned between ethyl acetate and H_2O. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by HPLC (10-45% acetonitrile in H_2O, 0.1% CF_3CO_2H) to give the corresponding trifluoroacetate salt which was converted to the free base to give the titled compound (60 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.15 (s, 1H), 7.06 (dd, J = 2.1, 8.5 Hz, 1H); 6.65 (d, J = 8.5, Hz, 1H); 3.27 (m, 1H); 3.11 (s, 2H); 2.15-2.05 (m, 2H); 2.00-1.91 (m, 2H); 1.90-1.80 (m, 2H); 1.75-1.56 (m, 2H).

APCI-MS: m/z 238(MH^+).

Example 1

2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-hydroxy-*N*-methylbenzamide



Step I

Methyl 2-hydroxy-4[(4-methoxybenzyl)oxy]benzoate

A mixture of methyl 2,4-dihydroxybenzoate (3.36 g, 20.0 mmol), p-methoxybenzyl chloride (3.29 g, 21.0 mmol) and K_2CO_3 (2.9 g, 21.0 mmol) in acetone (40 mL) was refluxed over night, cooled to room temperature, filtered and concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with H_2O. The organic layer was dried

over Na_2SO_4, filtered and concentrated. The residue was crystallized from methanol to give the sub titled compound (2.5 g).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.76 (d, J = 8.9 Hz, 1H); 7.39 (m, 2H); 6.94 (m, 2H); 6.55 (d, J = 2.5 Hz, 1H); 6.52 (dd, J = 2.5, 8.9 Hz, 1H); 5.00 (s, 2H); 3.99 (s, 3H); 3.84 (s, 3H).
Reference: V. Percec, D. Tomazos *J. Mater. Chem.* **1993**, *3*, 643-650.

Step II

2-Hydroxy-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide

To a suspension of methyl 2-hydroxy-4[(4-methoxybenzyl)oxy]benzoate (500 mg, 1.73 mmol) in methanol (15 mL) was added 40% aqueous methyl amine (3 mL) at 0 ^{0}C and the reaction mixture was stirred at room temnperature over the weekend. The volatiles were removed in vacuo to give the subtitled compound (500 mg).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 8.60 (m, 1H); 7.70 (d, J = 8.8 Hz, 1H); 7.38-7.33 (m, 2H); 6.96-6.91 (m, 2H); 6.49 (dd, J = 2.6, 8.8 Hz, 1H); 6.42 (d, J = 2.6 Hz, 1H); 5.00 (s, 2H); 3.75 (s, 3H); 2.77 (d, J = 4.6 Hz, 3H).
APCI-MS: m/z 288(MH^+).

Step III

4-[(4-Methoxybenzyl)oxy]-*N*-methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide

A mixture of (2S)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (151 mg, 0.584 mmol), 2-hydroxy-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide (168 mg, 0.584 mmol) and Cs_2CO_3 (228 mg, 0.7 mmol) in DMF (4 mL) was stirred at room temperature over night. The reaction mixture was partioned between ethyl acetate and H_2O. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-90% ethyl acetate in petroleum benzene) to give the subtitled compound (150 mg).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 7.90 (m, 1H); 7.75 (d, *J* = 8.7 Hz, 1H); 7.35 (d, *J* = 8.6 Hz, 2H); 6.96-6.91 (m, 2H); 6.74 (d, *J* = 2.3 Hz, 1H); 6.69 (dd, *J* = 2.3, 8.7 Hz, 1H); 5.12 (s, 2H); 4.48 (dd, *J* = 2.5, 11.5 Hz, 1H); 4.02 (dd, *J* = 6.0, 11.5 Hz, 1H); 3.75 (s, 3H); 3.42 (m, 1H); 2.86 (t, *J* = 4.9 Hz, 1H); 2.79 (d, *J* = 4.7 Hz, 3H); 2.73 (dd, *J* = 2.7, 5.0 Hz, 1H).

APCI-MS: m/z 344(MH^+).

Step IV

2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide

A mixture of (5-chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amine (25 mg, 0.105 mmol) and 4-[(4-methoxybenzyl)oxy]-*N*-methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide (36.3 mg, 0.105 mmol) in ethanol (2 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in CH_2Cl_2, 0.2% NH_4OH) to give the subtitled compound (15 mg).

APCI-MS: m/z 581(MH^+).

Step V

2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-hydroxy-*N*-methylbenzamide

2-({(2S)-3-[(5-chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide (15 mg, 0.026 mmol) was treated with 10% CF_3CO_2H in CH_2Cl_2 (3 mL) at room temperature for 20 minutes. The volatiles were removed in vacuo and the residue was purified by HPLC (10-50% CH_3CN in H_2O, 0.2% NH_4OH) to give the titled compound (6 mg).

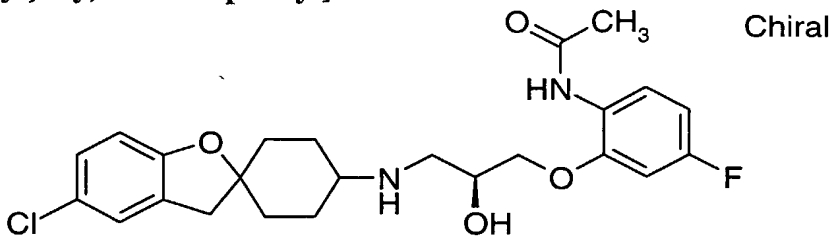
^{1}H-NMR (CD_3OD, 400 MHz): δ 7.79 (d, *J* = 8.6 Hz, 1H); 7.13 (m, 1H); 7.02 (dd, *J* = 2.3, 8.5 Hz, 1H); 6.61 (d, *J* = 8.5 Hz, 1H); 6.51 (d, *J* = 2.2 Hz, 1H); 6.47 (dd, *J* = 2.2, 8.6 Hz, 1H); 4.21-4.04 (m, 3H); 3.07 (s, 2H); 2.92 (s, 3H); 2.87 (dd, *J* = 4.3, 12.2 Hz, 1H); 2.77

(dd, J = 7.5, 12.2 Hz, 1H); 2.69 (m, 1H); 2.01 (m, 2H); 1.90 (m, 2H); 1.78 (m, 2H); 1.39 (m, 2H).

APCI-MS: m/z 461(MH^+).

Example 2

***N*-2-({(2S)-3-[5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-fluorophenyl]acetamide**



Step I

***N*-(4-Fluoro-2-hydroxyphenyl)acetamide**

A mixture of 5-fluoro-2-nitrophenol (5 g, 31.8 mmol), acetic anhydride (4.86 g, 47.7 mmol) and platinum on carbon (5%, 200 mg) in methanol was hydrogenated at 35 psi for 3 hours. The catalyst was filtered off and the residue was purified by silica gel flash chromatography to give the subtitled compound (4.7 g).

^{1}H-NMR (CD_3OD, 300 MHz): δ 7.56-7.51 (m, 1H); 6.61-6.50 (m, 2H); 2.15 (s, 3H).

APCI-MS: m/z 170(MH^+).

Step II

***N*-{4-Fluoro-2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide**

A mixture of *N*-(4-fluoro-2-hydroxyphenyl)acetamide (1.69 g, 10.0 mmol), (2S)-oxiran 2-ylmethyl-3-nitrobenzenesulfonate (2.59 g, 10.0 mmol) and Cs_2CO_3 (4.87 g, 15.0 mmol) in DMF (15 mL) was stirred at room temperature for 2 hours. The reaction mixture was partitioned between ethyl acetate and H_2O. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash chromatography to give the subtitled compound (1.35 g).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.33-8.29 (m, 1H); 7.71 (br. s, 1H); 6.74-6.66 (m, 2H); 4.39-4.36 (m, 1H); 3.95-3.90 (m, 1H); 3.41-3.39 (m, 1H); 2.99-2.97 (m, 1H); 2.80 (m, 1H).
APCI-MS: m/z 226(MH^+).

Step III

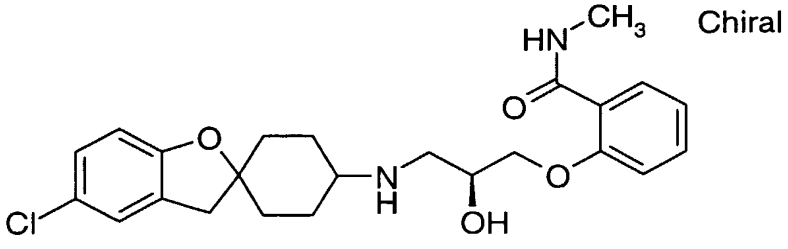
***N*-2-({(2S)-3-[5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-fluorophenyl]acetamide**

A mixture of (5-chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amine (11.6 mg, 0.049 mmol) and *N*-{4-fluoro-2-[(2S)-oxiran-2-ylmethoxy] phenyl}acetamide (11 mg, 0.049 mmol) in ethanol (1.5 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5 % methanol in CH_2Cl_2, 0.2% NH_4OH) to give the titled compound (10 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.87 (dd, J = 6.2, 8.9 Hz, 1H); 7.13 (m, 1H); 7.05 (dd, J = 2.3, 8.5 Hz, 1H); 6.86 (dd, J = 2.7, 10.5 Hz, 1H); 6.71-6.64 (m, 1H); 6.61 (d, J = 8.5 Hz, 1H); 4.14-4.07 (m, 2H); 3.99 (dd, J = 7.1, 10.6 Hz, 1H); 3.08 (s, 2H); 2.89 (dd, J = 4.0, 12.0 Hz, 1H); 2.77 (dd, J = 7.6, 12.0 Hz, 1H); 2.69 (m, 1H); 2.17 (s, 3H); 2.04 (m, 2H); 1.90 (m, 2H); 1.78 (m, 2H); 1.40 (m, 2H).
APCI-MS: m/z 463(MH^+).

Example 3

2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-*N*-methylbenzamide



Step I

2-Hydroxy-*N*-methylbenzamide

A solution of methyl salicylate (5.16 mL, 40 mmol) in methanol (10 mL) was added dropwise to aqueous 40% methylamine (18.1 mL, 210 mmol) at 0 ^{0}C. After the addition was completed the reaction mixture was stirred at room temperature overnight. The volatiles were removed in vacuo to give the subtitled compound (5.48 g).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.70 (dd, J = 1.5, 7.9 Hz, 1H); 7.38-7.32 (m, 2H); 6.90-6.83 (m, 2H); 2.85 (s, 3H).

Step II

***N*-Methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide**

A mixture of (2S)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate (388.5 mg, 1.50 mmol), 2-hydroxy-*N*-methylbenzamide (226.5 mg, 1.50 mmol) and Cs_2CO_3 (586 mg, 1.80 mmol) in DMF (6 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and H_2O. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-50% ethyl acetate in petroleum benzene) to give the subtitled compound (284 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.39 (m, 1H); 7.90 (br.s, 1H); 7.06-6.98 (m, 2H); 6.95-6.89 (m, 1H); 4.38 (dd, J = 2.5, 11.4 Hz, 1H); 3.98 (dd, J = 6.0, 11.4 Hz, 1H); 3.40 (m, 1H); 2.97 (t, J = 5.0 Hz, 1H); 2.81 (dd, J = 2.7, 4.8 Hz, 1H); 2.21 (s, 3H).
APCI-MS: m/z 208(MH^+).

Step III

2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-*N*-methylbenzamide

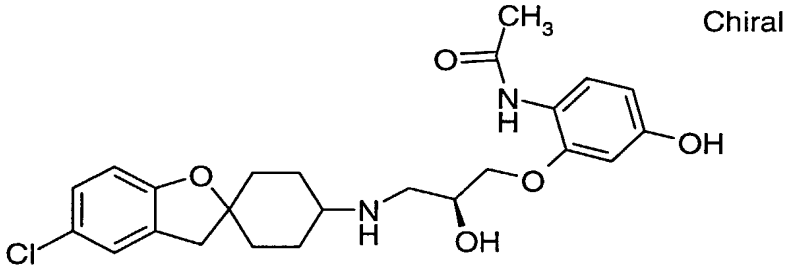
A mixture of (5-chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amine (14 mg, 0.059 mmol) and *N*-methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide (12.2 mg, 0.059 mmol) in ethanol (1.5 mL) was stirred at 80 ^{0}C over night. The volatiles were removed in

vacuo and the residue was purified by HPLC (10-50% CH_3CN in H_2O, 0.2% NH_4OH) to give the titled compound (5 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.86 (dd, J = 1.7, 7.7 Hz, 1H); 7.50-7.45 (m, 1H); 7.15 (m, 2H); 7.10-7.05 (m, 1H); 7.03 (dd, J = 2.2, 8.5 Hz, 1H); 6.61 (d, J = 8.5 Hz, 1H); 4.24 (m, 1H); 4.15 (m, 2H); 3.07 (s, 2H); 2.95 (s, 3H); 2.89 (m, 1H); 2.80 (m, 1H); 2.69 (m, 1H); 2.02 (m, 2H); 1.90 (m, 2H); 1.75 (m, 2H); 1.39 (m, 2H).
APCI-MS: m/z 445(MH^+).

Example 4

***N*-[2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-hydroxyphenyl]acetamide**



Step I

(1Z)-1-(2,4-Dihydroxyphenyl)ethanone oxime

1-(2,4-Dihydroxyphenyl)ethanone (4.5 g, 29.6 mmol) was dissolved in pyridine (17 mL). Hydroxylamine hydrochloride (2.1 g, 29.6 mmol) was added in small portions over 10 minutes. The reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and H_2O. The organic layer was washed with H_2O, 0.2 M HCl and then concentrated. The oily residue was treated with water, evaporated to yield a white semi-solid residue which was treated with toluene and evaporated to give the subtitled compound (4.8 g) as a white solid.

APCI-MS: m/z 168(MH^+).

Step II

2-Methyl-1,3-benzoxazol-6-ol

To a cooled (5 ^{0}C) solution of (1Z)-1-(2,4-dihydroxyphenyl)ethanone oxime (9.7 g, 57.7 mmol) in acetonitrile (65 mL) and dimethylacetamide (11 mL) was added phosphorous oxychloride (5.6 mL, 60.3 mmol) dropwise. The temperature was not allowed to exceed 10 ^{0}C during the addition. After 1 hour stirring at room temperature the yellow slurry was poured into a mixture of aqueous $NaHCO_3$ and ice. The resulting precipitate was filtered off and dried to give the subtitled compound (6.3 g).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 7.40 (d, 1H); 6.98 (s, 1H); 6.89 (d, 1H); 2.45 (s, 3H).
APCI-MS: m/z 150(MH^+).

Step III

2-Methyl-1,3-benzoxazol-6-yl acetate

A slurry of methyl-1,3-benzoxazol-6-ol (7.1 g, 47.8 mmol) in THF 150 mL) was cooled to 10 ^{0}C and Et_3N (5.8 mL, 81.3 mmol) was added in one portion, followed by the addition of acetyl chloride (11.3 mL, 81.6 mmol) in small portions. After addition was completed the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4, filtered and concentrated to give the subtitled compound (8.2 g).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 7.65 (d, 1H); 7.47 (s, 1H); 7.15 (d, 1H); 2.60 (s, 3H); 2.24 (s, 3H).

Step IV

4-(Acetylamino)-3-hydroxyphenyl acetate

To a solution of 2-methyl-1,3-benzoxazol-6-yl acetate (5.05 g, 28.8 mmol) in THF (100 mL) a mixture trifluoroacetic acid/water (4 ml/10 mL) was added. The reaction mixture was stirred at room temperature for 16 hours, then saurated aqueous $NaHCO_3$ (150 mL) was added. The mixture was extracted with ethyl acetate (150 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give the subtitled compound (4.0 g)

Step V

4-(Acetylamino)-3-[(2S)-oxiran-2-ylmethoxy]phenyl acetate

A solution of 4-(acetylamino)-3-hydroxyphenyl acetate (669 mg, 3.2 mmol), (2S)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate (748 mg, 2.9 mmol) and Cs_2CO_3 (1.05 g, 3.2 mmol) in 1-methyl-pyrrolidinone (10 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4, filtered and concentrated to give a yellow oil which was suspended in methanol/diethyl ether. The precipitate was filtered off and dried to give the subtitled compound (296 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.40 (d, 1H); 7.80 (s, 1H); 6.78 (m, 2H); 4.39 (m, 1H); 3.92 (m, 1H); 3.40 (m, 1H); 2.98 (t, 1H); 2.80 (m, 1H); 2.25 (s, 3H); 2.20 (s, 3H).

Step VI

***N*-[2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-hydroxyphenyl]acetamide**

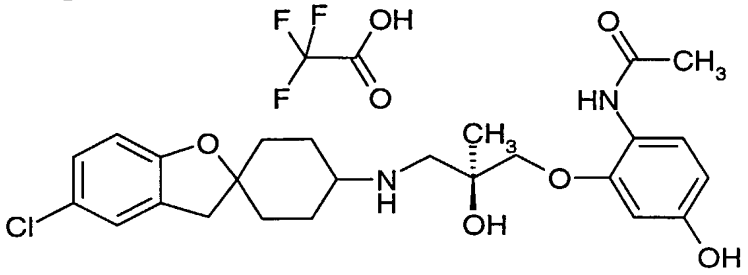
A mixture of (5-chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amine (14 mg, 0.06 mmol) and 4-(acetylamino)-3-[(2S)-oxiran-2-ylmethoxy]phenyl acetate (16 mg, 0.06 mmol) in ethanol (1.5 mL) was stirred at 80 ^{0}C over the weekend. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3.5% methanol in CH_2Cl_2, 0.2% NH_4OH) to give the titled compound (15 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.53 (d, J = 8.6 Hz, 1H); 7.13 (m, 1H); 7.03 (dd, J = 2.3, 8.5 Hz, 1H); 6.61 (d, J = 8.5 Hz, 1H); 6.47 (d, J = 2.5 Hz, 1H); 6.36 (dd, J = 2.5, 8.6 Hz, 1H); 4-11-4.04 (m, 1H); 4.02 (dd, J = 4.0, 9.8 Hz, 1H); 3.95 (dd, J = 6.0, 9.8 Hz, 1H); 3.08 (s, 2H); 2.89 (dd, J = 4.2, 12.2 Hz, 1H); 2.75 (dd, J = 8.1, 12.2 Hz, 1H); 2.68 (m, 1H); 2.11 (s, 3H); 2.02 (m, 2H); 1.90 (m, 2H); 1.78 (m, 2H); 1.39 (m, 2H).

APCI-MS: m/z 461(MH^+).

Example 5

***N*-[2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxy-2-methylpropyl}oxy)-4-hydroxyphenyl]acetamide (trifluoro acetate)**



Step I

2-Methyl-1,3-benzoxazol-6-yl benzoate:

To a stirred suspension of 2-methyl-1,3-benzoxazol-6-ol (2.99 g, 20 mmol) in dichloromethane (50 mL) was added triethylamine (4.05 g, 5.58 mL, 40 mmol). A solution of benzoyl chloride (3.09 g, 2.56 mL, 22 mmol) in dichloromethane (20 mL) was added dropwise over about 10 minutes. The reaction mixture was stirred at room temperature for 2.5 hours, then washed with water (2 x 50 mL), and dried over Na_2SO_4, filtered and concentrated in vacuo to give the subtitled compound as colourless solid (5.05 g, 20 mmol, quant.).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.22 (m, 2H), 7.66 (m, 2H), 7.53 (m, 2H), 7.40 (d, 1H), 7.16 (dd, 1H), 2.65 (s, 3H).

APCI-MS: m/z 254 [MH^+].

Step II

4-(Acetylamino)-3-hydroxyphenyl benzoate:

To a solution of 2-methyl-1,3-benzoxazol-6-yl benzoate (5.05 g, 20 mmol) in THF (100 mL) a mixture trifluoroacetic acid/water (4 ml/10 mL) was added. The reaction mixture was stirred at room temperature for 16 hours, then saurated aqueous $NaHCO_3$ (150 mL) was added. The mixture was extracted with ethyl acetate (150 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give the subtitled compound.

^{1}H-NMR (400 MHz, acetone-d_6): δ 9.76 (br.s, 1H), 9.32 (br.s, 1H), 8.15 (m, 2H), 7.71 (m, 1H), 7.60 (m, 2H), 7.47 (d, 1H), 6.85 (m, 1H), 6.75 (m, 1H), 2.20 (s, 3H).
APCI-MS: m/z 272 [MH^+].

Step III

[(2S)-2-Methyloxiranyl]methyl3-nitrobenzenesulfonate

To an oven-dried 1000 mL three-necked flask was added powdered activated molecular sieves (8.0 g, 4Å) and CH_2Cl_2 (440 mL), D-(-)-diisopropyl tartrate (4 mL, 14.2 mmol) and 2-methyl-2-propene-1-ol (20 mL, 240 mmol) was added and the mixture was cooled to –20 ^{0}C. Titanium tetraisopropoxide (3.5 mL, 11.9 mmol) was added with a few millilitres of CH_2Cl_2 and the mixture was stirred at –20 ^{0}C for 30 minutes. Cumene hydroperoxide (75 mL, 430 mmol) was added dropwise over 1.5 hours maintaining the temperature at –20 ^{0}C. The mixture was stirred at this temperature overnight. Trimethyl phosphite (40 mL, 340 mmol) was added dropwise over 5 hours maintaining the temperature at –20 ^{0}C. Triethylamine (50 mL, 360 mmol) and DMAP (3.48 g, 28.5 mmol) was added followed by a solution of 3-nitrobenzenesulphonyl chloride (47 g, 212 mmol) in CH_2Cl_2 (400 mL). The temperature was raised to –10 ^{0}C and the mixture was stirred at this temperature overnight. After removing the external cooling vessel, the reaction mixture was filtered through celite. The organic phase was washed with 10% tartaric acid (500 mL), saturated $NaHCO_3$ (300 mL) and brine (300 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give 150 g of a yellow oil. The crude material was purified by silica gel flash chromatography (0-50% ethyl acetate in heptane) to give the subtitled compound (48.8 g).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.79-8.75 (m, 1H); 8.52 (ddd, J = 1.1, 2.3, 8.3 Hz, 1H); 8.25 (ddd, J = 1.1, 1.8, 7.8 Hz, 1H); 7.81 (t, J = 8.5 Hz, 1H); 4.28 (d, J = 11.3 Hz, 1H); 4.05 (d, J = 11.3 Hz, 1H); 2.73 (d, J = 4.4 Hz, 1H); 2.67 (d, J = 4.4 Hz, 1H); 1.56 (s, 3H).

Step IV:

4-(Acetylamino)-3-{[(2S)-2-methyloxiran-2-yl]methoxy}phenyl benzoate

A mixture of 4-(acetylamino)-3-hydroxyphenyl benzoate (2.71 g, 10 mmol), [(2*S*)-2-methyloxiran-2-yl]methyl3-nitrobenzenesulfonate (2.73 g, 10 mmol) and Cs_2CO_3 (3.57 g, 11 mmol) in 1-methylpyrrolidin-2-one (35 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash chromatography (ethyl acetate/*n*-heptane) to give the sub titled compound as a colourless solid (1.31g, 3.9 mmol, 39 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.41 (d, 1H), 8.18 (m, 2H), 7.91 (br.s, 1H), 7.63 (m, 1H), 7.50 (m, 2H), 6.83 (m, 1H), 4.15 (d, *J* = 10.8 Hz, 1H), 4.03 (d, *J* = 10.8 Hz, 1H), 3.99 (d, *J* = 10.8 Hz, 1H), 2.92 (d, *J* = 4.6 Hz, 1H), 2.78 (d, *J* = 4.6 Hz, 1H), 2.22 (s, 3H), 1.48 (s, 3H).

APCI-MS: m/z 342 [MH^+].

Step V

***N*-[2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxy-2-methylpropyl}oxy)-4-hydroxyphenyl]acetamide (trifluoro acetate)**

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-amine (20 mg, 0.084 mmol) and 4-(acetylamino)-3-{[(2S)-2-methyloxiran-2-yl]methoxy}phenyl benzoate (29 mg, 0.084 mmol) in ethanol (1.5 mL) was stirred at 80 ^{0}C over night, 2 drops conc NaOEt was added and the mixture was stirred at room temperature for 4 hours. The volatiles were removed in vacuo and the residue was purified by HPLC (10-80 % acetonitrile in water, 0.1% CF_3CO_2H) to give the titled compound (20 mg).

^{1}H-NMR (400 MHz, CD_3OD): δ 7.19-7.13 (m, 2H); 7.08-7.03 (m, 1H); 6.67-6.62 (m, 1H); 6.50 (m, 1H); 6.43-6.39 (m,. 1H); 3.90 (m, 2H); 3.38-3.00 (m, 5H); 2.20 (m, 2H); 2.23 (s, 3H); 2.22-1.90 (m, 2H); 1.82 (m, 2H); 1.68 (m, 2H); 1.42 (s, 3H).

APCI-MS: m/z 475 [MH^+].

THP-1 Chemotaxis Assay

Introduction

The assay measures the chemotactic response elicited by MIP-1α chemokine in the human monocytic cell line THP-1. Compounds are evaluated by their ability to depress the chemotactic response to a standard concentration of MIP-1α chemokine.

Methods

Culture of THP-1 cells

Cells are thawed rapidly at 37°C from frozen aliquots and resuspended in a 25 cm flask containing 5 ml of RPMI-1640 medium supplemented with Glutamax and 10% heat inactivated fetal calf serum without antibiotics (RPMI+10%HIFCS). At day 3 the medium is discarded and replaced with fresh medium.

THP-1 cells are routinely cultured in RPMI-1640 medium supplemented with 10% heat inactivated fetal calf serum and glutamax but without antibiotics. Optimal growth of the cells requires that they are passaged every 3 days and that the minimum subculture density is $4x10^5$ cells/ml.

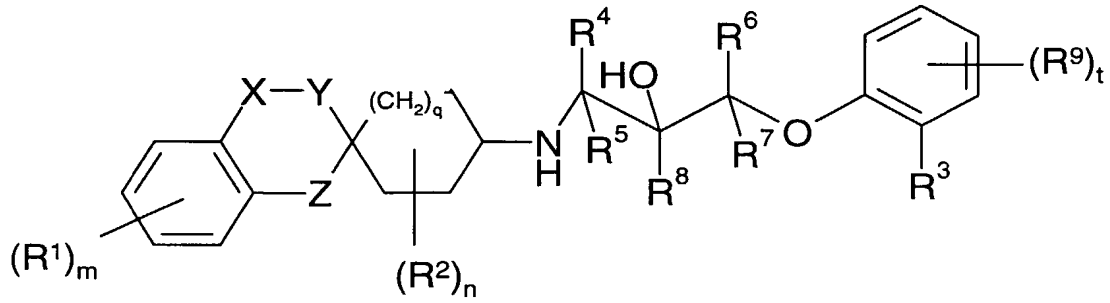
Chemotaxis assay

Cells are removed from the flask and washed by centrifugation in RPMI + 10%HIFCS + glutamax. The cells are then resuspended at $2x10^7$ cells/ml in fresh medium (RPMI + 10%HIFCS + glutamax) to which is added calcein-AM (5 µl of stock solution to 1 ml to give a final concentration of $5x10^{-6}$M). After gentle mixing the cells are incubated at 37°C in a CO_2 incubator for 30 minutes. The cells are then diluted to 50 ml with medium and washed twice by centrifugation at 400xg. Labelled cells are then resuspended at a cell concentration of $1x10^7$ cells/ml and incubated with an equal volume of MIP-1α antagonist (10^{-10}M to 10^{-6}M final concentration) for 30 minutes at 37°C in a humidified CO_2 incubator.

Chemotaxis is performed using Neuroprobe 96-well chemotaxis plates employing 8 μm filters (cat no. 101-8). Thirty microlitres of chemoattractant supplemented with various concentrations of antagonists or vehicle are added to the lower wells of the plate in triplicate. The filter is then carefully positioned on top and then 25μl of cells preincubated with the corresponding concentration of antagonist or vehicle is added to the surface of the filter. The plate is then incubated for 2 hours at 37°C in a humidified CO_2 incubator. The cells remaining on the surface are then removed by adsorption and the whole plate is centrifuged at 2000 rpm for 10 minutes. The filter is then removed and the cells that have migrated to the lower wells are quantified by the fluorescence of cell associated calcein-AM. Cell migration is then expressed in fluorescence units after subtraction of the reagent blank and values are standardized to % migration by comparing the fluorescence values with that of a known number of labelled cells. The effect of antagonists is calculated as % inhibition when the number of migrated cells is compared with vehicle.

CLAIMS

1. A compound of formula



(I)

wherein

m is 0, 1, 2, 3 or 4;

each R^1 independently represents halogen, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy or sulphonamido;

either X represents a bond, $-CH_2-$, -O- or -C(O)- and Y represents a bond, $-CH_2-$, -O- or -C(O)-, or X and Y together represent a group $-CH=C(CH_3)-$ or $-C(CH_3)=CH-$, and Z represents a bond, -O-, -NH- or $-CH_2-$, provided that only one of X, Y and Z can represent a bond at any one time and provided that X and Y do not both simultaneously represent –O- or -C(O)-;

n is 0, 1 or 2;

each R^2 independently represents halogen or C_1-C_6 alkyl;

q is 0 or 1;

R^3 represents $-NHC(O)R^{10}$, $-C(O)NR^{11}R^{12}$ or $-COOR^{12a}$;

R^4, R^5, R^6, R^7 and R^8 each independently represent a hydrogen atom or a C_1-C_6 alkyl group;

t is 0, 1 or 2;

each R^9 independently represents halogen, cyano, hydroxyl, carboxyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, or C_1-C_6 alkyl optionally substituted by at least one substituent selected from carboxyl and C_1-C_6 alkoxycarbonyl;

R^{10} represents a group C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, adamantyl, C_5-C_6 cycloalkenyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each of which may be optionally substituted by one or more substituents independently selected from nitro, hydroxyl, oxo, halogen, carboxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, phenyl and -NHC(O)-R^{13}, or

R^{10} represents a group $-NR^{14}R^{15}$ or $-O-R^{16}$;

R^{11} and R^{12} each independently represent (i) a hydrogen atom, (ii) a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur and optionally further comprising a bridging group, the ring being optionally substituted with at least one substituent selected from halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl and C_1-C_6 haloalkyl, (iii) a C_1-C_6 alkyl group optionally substituted by at least one substituent selected from halogen, amino, hydroxyl, C_1-C_6 haloalkyl, carboxyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkylcarbonylamino and a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur and optionally further comprising a bridging group, the ring being optionally substituted with at least one substituent selected from halogen, hydroxyl, oxo, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl and C_1-C_6 haloalkyl, or (iv) C_1-C_6 alkylsulphonyl, or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom and that is optionally fused to a benzene ring to form a 8- to 11-membered ring system, the heterocyclic ring or ring system being optionally substituted with at least one substituent selected from halogen, hydroxyl, amido, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonylamino, C_1-C_6 alkylaminocarbonyl, di-C_1-C_6 alkylaminocarbonyl, phenyl, halophenyl, phenylcarbonyl, phenylcarbonyloxy and hydroxydiphenylmethyl;

R^{12a} represents a hydrogen atom or a C_1-C_6 alkyl group;

R^{13} represents a C_1-C_6 alkyl, amino or phenyl group;

R^{14} and R^{15} each independently represent a hydrogen atom, or a group C_1-C_6 alkyl, C_1-C_6 alkylsulphonyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted as defined above for R^{10}, or

R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom, the heterocyclic ring being optionally substituted by at least one hydroxyl; and

R^{16} represents a hydrogen atom, or a group C_1-C_6 alkyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted as defined above for R^{10};

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein X and Y have the meanings shown in the following table:

X	Y
bond	O
O	bond
CH_2	bond
bond	CH_2

3. A compound according to claim 1 or claim 2, wherein Z represents -O- or -CH_2-.

4. A compound according to any one of claims 1 to 3, wherein q is 1.

5. A compound according to any one of claims 1 to 4, wherein R^3 represents $-NHC(O)R^{10}$ or $-C(O)NR^{11}R^{12}$.

6. A compound according to any one of claims 1 to 5, wherein t is 1 and R^9 is located in the *para* position with respect to R^3.

7. A compound according to claim 1 selected from:

2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-hydroxy-*N*-methylbenzamide,

N-2-({(2S)-3-[5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-fluorophenyl]acetamide,

2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-*N*-methylbenzamide,

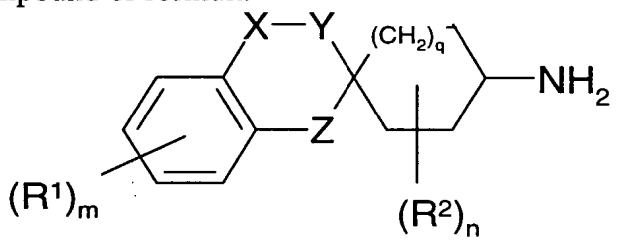
N-[2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-hydroxyphenyl]acetamide,

N-[2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxy-2-methylpropyl}oxy)-4-hydroxyphenyl]acetamide (trifluoro acetate),

and pharmaceutically acceptable salts and solvates of any one thereof.

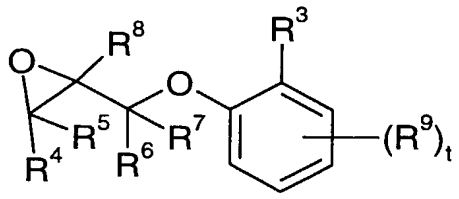
8. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined in claim 1 which comprises,

(a) reacting a compound of formula



(II)

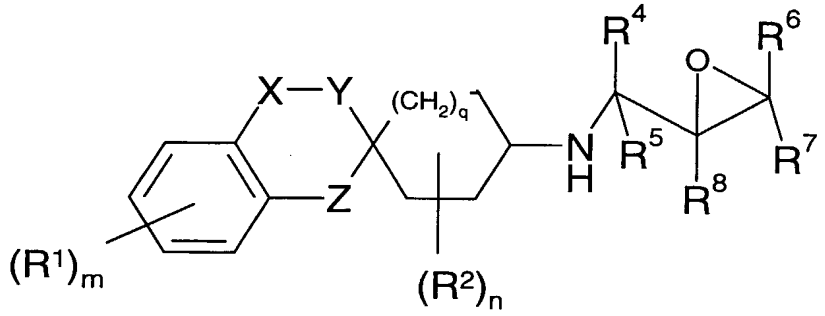
wherein m, R^1, n, R^2, q, X, Y and Z are as defined in formula (I), with a compound of formula



(III)

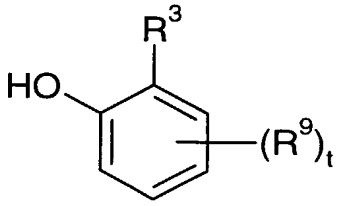
wherein R^3, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in formula (I); or

(b) reacting a compound of formula



(IV)

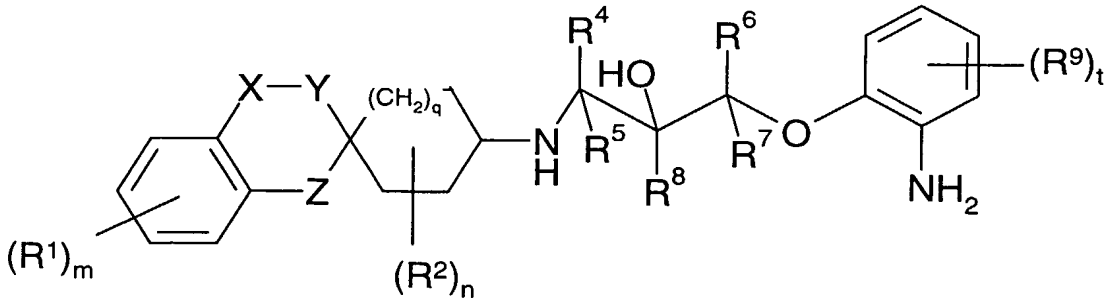
wherein m, R^1, n, R^2, q, X, Y, Z, R^4, R^5, R^6, R^7 and R^8 are as defined in formula (I), with a compound of formula



(V)

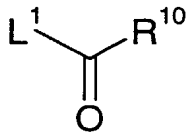
wherein R^3, t and R^9 are as defined in formula (I), in the presence of a suitable base; or

(c) when R^3 represents -NHC(O)R^{10}, reacting a compound of formula



(VI)

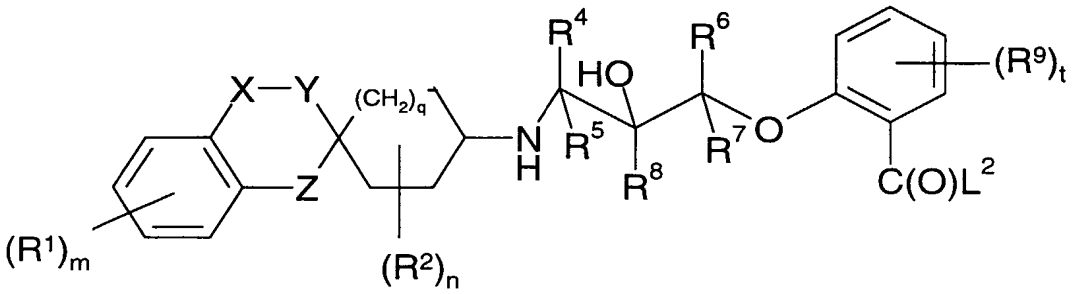
wherein m, R^1, n, R^2, q, X, Y, Z, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in formula (I), with a compound of formula



(VII)

wherein L^1 represents a leaving group and R^{10} is as defined in formula (I); or

(d) when R^3 represents -C(O)$NR^{11}R^{12}$, reacting a compound of formula



(VIII)

wherein L^2 represents a leaving group and m, R^1, n, R^2, q, X, Y, Z, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in formula (I), with a compound of formula (IX), $NHR^{11}R^{12}$, wherein R^{11} and R^{12} are as defined in formula (I); or

(e) when R^3 represents -NHC(O)R^{10}, R^{10} represents –$NR^{14}R^{15}$ and R^{14} and R^{15} both represent hydrogen, reacting a compound of formula (VI) as defined in (c) above with potassium cyanate;

and optionally after (a), (b), (c), (d) or (e) forming a pharmaceutically acceptable salt or solvate.

9. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. A process for the preparation of a pharmaceutical composition as claimed in claim 9 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 with a pharmaceutically acceptable adjuvant, diluent or carrier.

11. A compound of formula (I) or a pharmaceutically-acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 for use in therapy.

12. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial.

13. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in treating rheumatoid arthritis.

14. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in treating chronic obstructive pulmonary disease.

15. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in treating asthma.

16. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in treating multiple sclerosis.

17. A method of treating an inflammatory disease which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7.

18. A method of treating an airways disease which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001476

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 307/94, A61K 31/343, A61P 11/06, A61P 11/08, A61P 19/02, A61P 29/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9825605 A1 (MERCK & CO., INC.), 18 June 1998 (18.06.1998) --	1-18
A	WO 9636625 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 21 November 1996 (21.11.1996) --	1-18
A	WO 9210096 A1 (T CELL SCIENCES, INC.), 25 June 1992 (25.06.1992) --	1-18
A	WO 9831364 A1 (MERCK & CO., INC.), 23 July 1998 (23.07.1998) --	1-18

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 February 2005	11 -02- 2005
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer EVA JOHANSSON/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001476

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0164213 A1 (SMITHKLINE BEECHAM CORPORATION), 7 Sept 2001 (07.09.2001)	1-18
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A	WO 0014086 A1 (LEUKOSITE, INC.), 16 March 2000 (16.03.2000)	1-18
	--	
P,A	WO 2004005295 A1 (ASTRAZENECA AB), 15 January 2004 (15.01.2004)	1-18
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2004/001476

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.: 17, 18
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 17 and 18 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic

.../...

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.

WO	9825605	A1	18/06/1998	AU	737107	B	09/08/2001
				AU	4954297	A	29/05/1998
				AU	5803398	A	03/07/1998
				CA	2271146	A	14/05/1998
				EP	0937244	A	25/08/1999
				GB	9703005	D	00/00/0000
				NZ	335885	A	26/01/2001
				US	6387232	B	14/05/2002
				US	5962462	A	05/10/1999
WO	9636625	A1	21/11/1996	AT	231501	T	15/02/2003
				AU	698028	B	22/10/1998
				AU	5895496	A	29/11/1996
				CA	2221357	A	21/11/1996
				DE	59610077	D	00/00/0000
				DK	828728	T	19/05/2003
				EP	0828728	A,B	18/03/1998
				SE	0828728	T3	
				ES	2191754	T	16/09/2003
				JP	11505236	T	18/05/1999
				PT	828728	T	30/06/2003
				SI	828728	T	00/00/0000
				US	5902824	A	11/05/1999
WO	9210096	A1	25/06/1992	AU	663066	B	28/09/1995
				AU	9127491	A	08/07/1992
				CA	2097826	A	07/06/1992
				EP	0561989	A	29/09/1993
				JP	6503829	T	28/04/1994
				KR	187327	B	01/05/1999
				US	5366986	A	22/11/1994
				US	5506247	A	09/04/1996
				US	5656659	A	12/08/1997
				US	5808109	A	15/09/1998
WO	9831364	A1	23/07/1998	AU	6133098	A	07/08/1998
				CA	2278309	A	23/07/1998
				EP	1003743	A	31/05/2000
				GB	9707490	D	00/00/0000
				JP	2001508798	T	03/07/2001
				US	6124319	A	26/09/2000
WO	0164213	A1	07/09/2001	AU	4339401	A	12/09/2001
WO	0014086	A1	16/03/2000	AU	2464999	A	27/03/2000
				CA	2342882	A	16/03/2000
				EP	1109804	A	27/06/2001
				JP	2002524458	T	06/08/2002
				US	6288083	B	11/09/2001
				US	6288084	B	11/09/2001
				US	6503926	B	07/01/2003
				US	20020161005	A	31/10/2002

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001476

WO	2004005295	A1	15/01/2004	AU	2002353713 A	00/00/0000
				CA	2462819 A	30/05/2003
				EP	1451356 A	01/09/2004
				SE	0202133 D	00/00/0000
				US	20050003361 A	06/01/2005